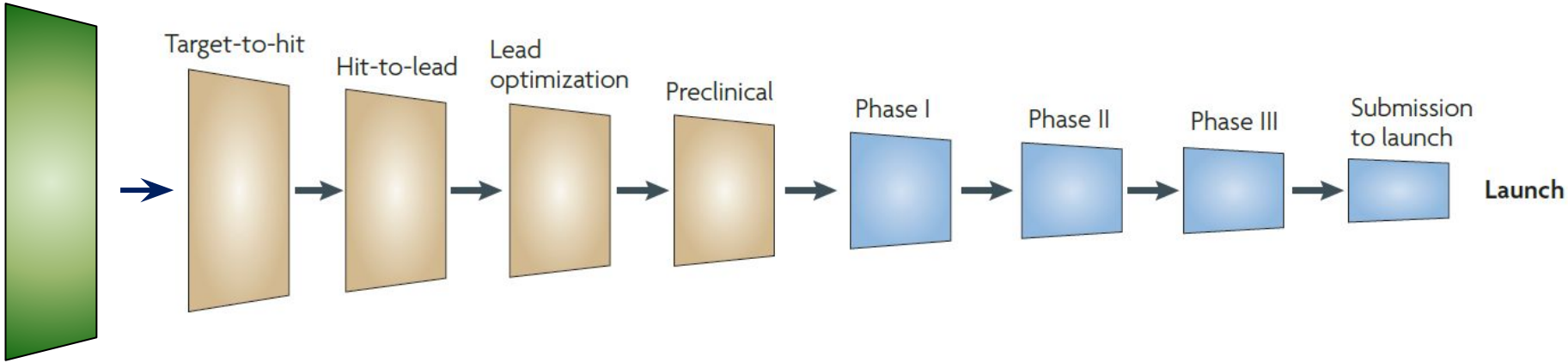
What can we do if there are no good targets

Mathematical and Computational Biology in Drug Discovery (MCBDD) Module II

Dr. Jitao David Zhang
March-April 2021

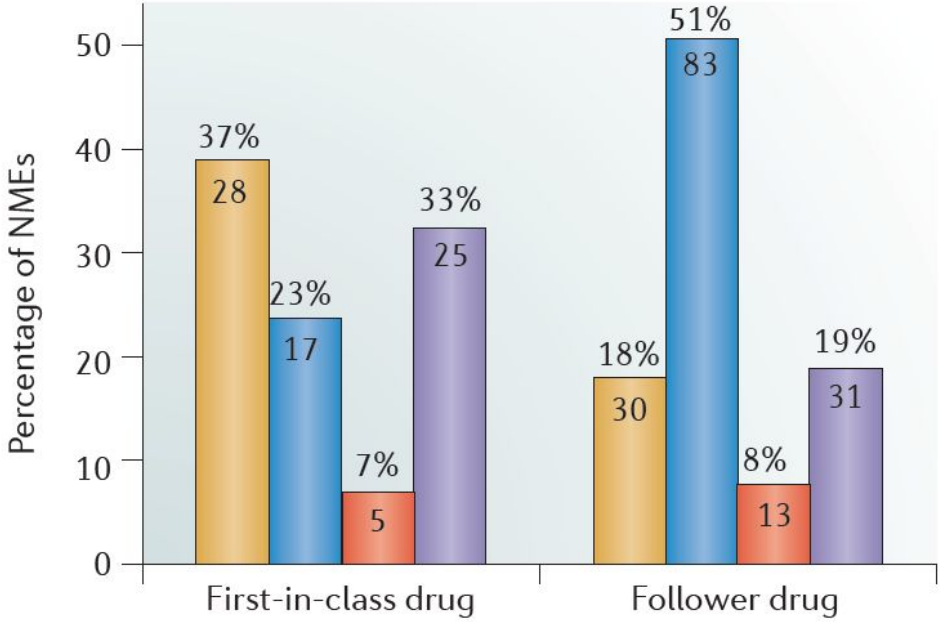
The linear view of drug discovery builds on target-based approaches

Target identification & assessment



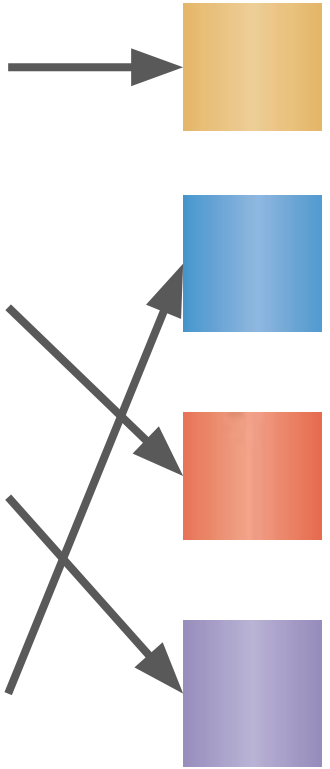
Five strategies when no good target is found

1. Phenotypic drug discovery
2. Natural products
3. Biologics
4. Interaction-based (multispecific) drug discovery
5. Drug repurposing or combination studies

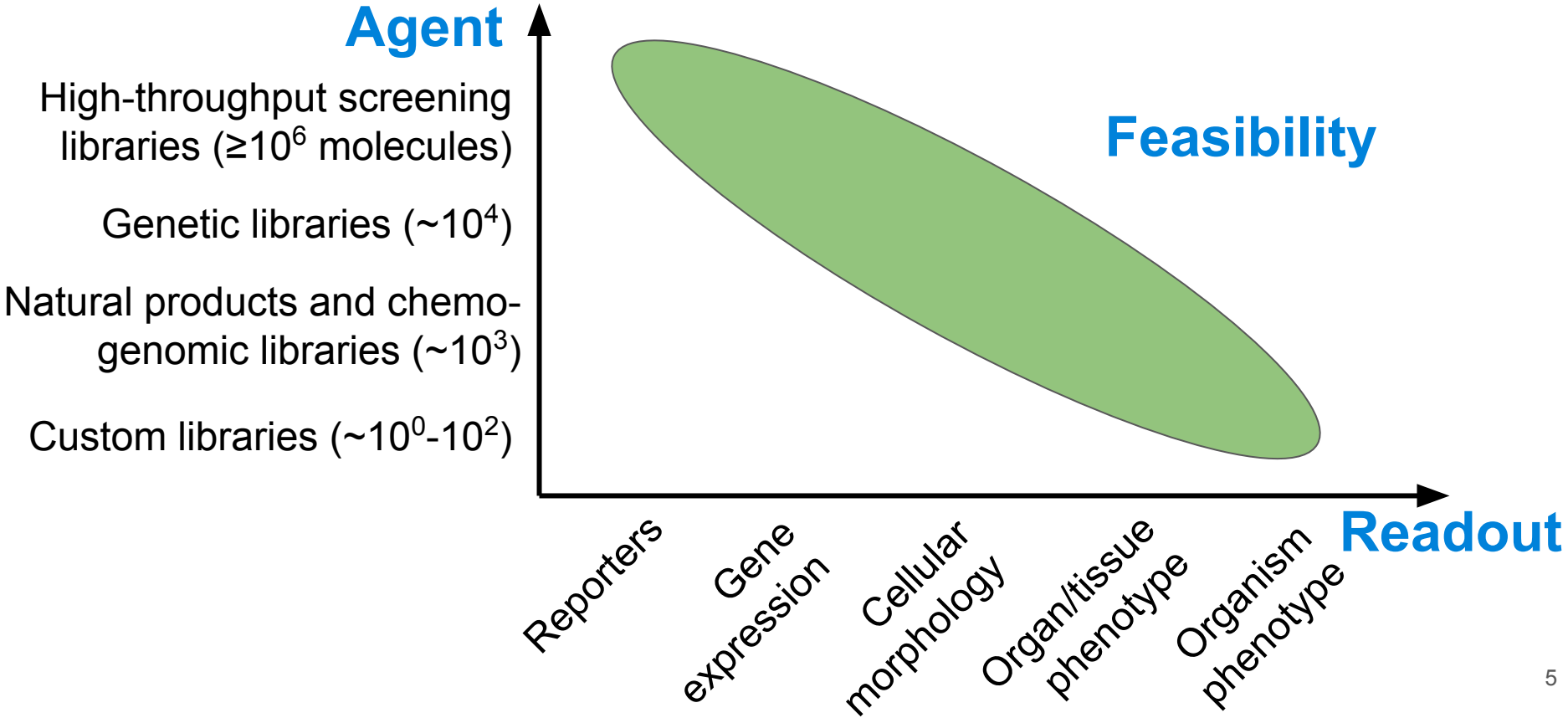


Connect the lines!

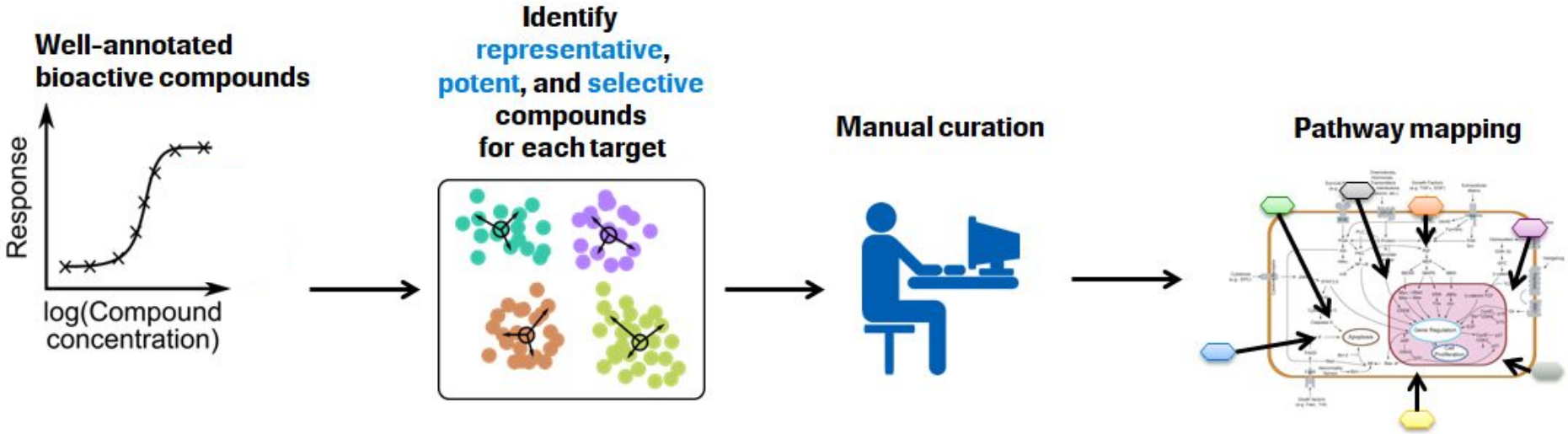
- Phenotypic screening
- Modified natural products
- Biologics
- Target-based screening



Phenotypic screenings by agent and readout

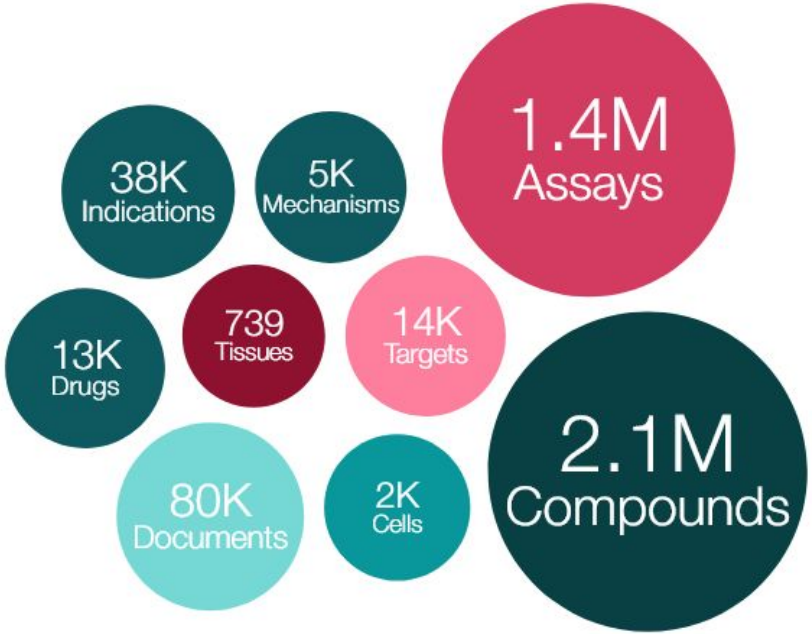


The Small-molecule PAthway Research Kit (SPARK)



The ChEMBL database

- An example of query: aspirin.
- Systematic and programmatic accession via ChEMBL API (source code).
- We can use **dose-response data** to annotate the *triplets* of compound, assay activity, and targets.

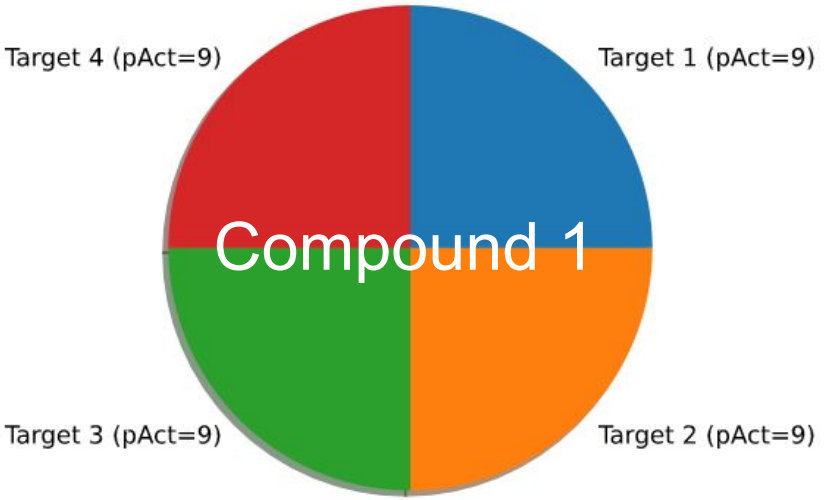


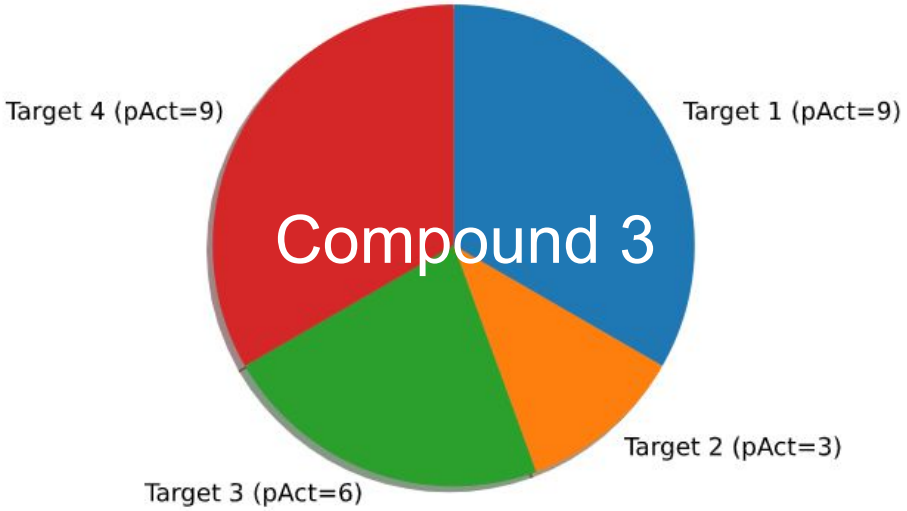
March 2021

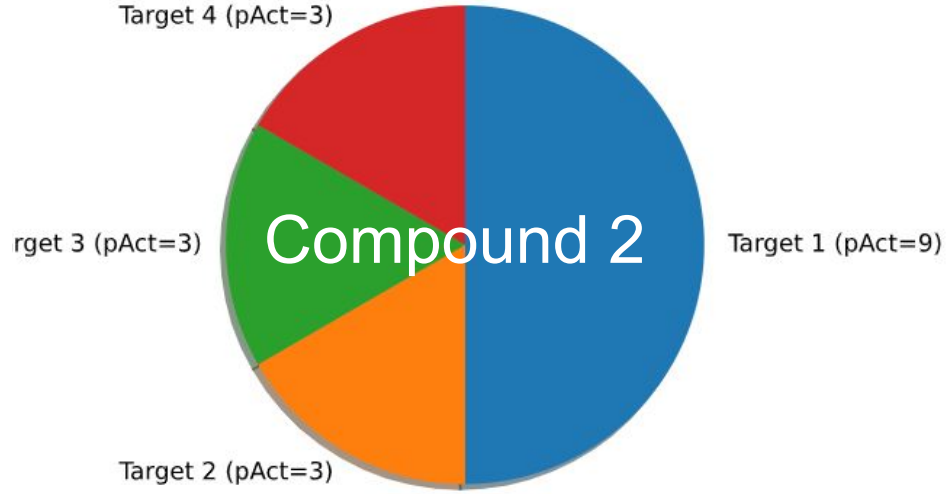
Discussion

1. Why do we care selecting *representative*, *potent*, and *selective* compounds for each target?
2. How to define following terms mathematically ...
    a. Representativity?
    b. Potency?
    c. Selectivity?

A toy example about how to quantify a compound's potency and selectivity

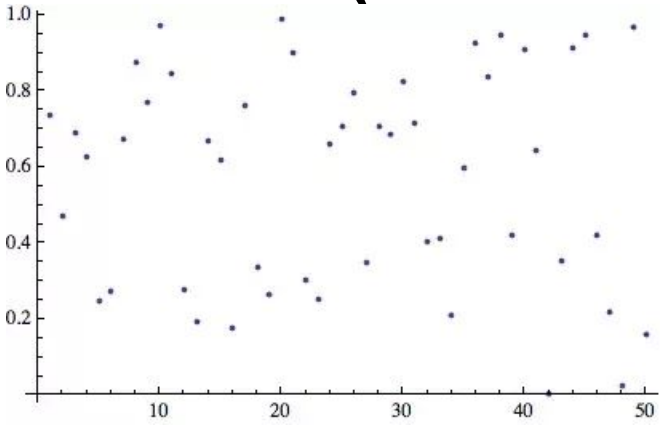




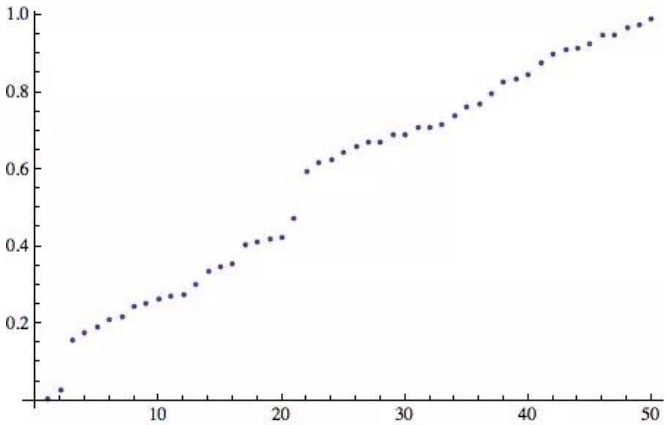


The Gini Index (a.k.a. Gini Coefficient)

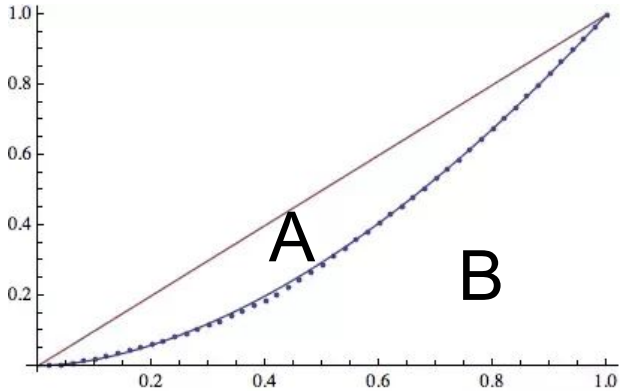
A random vector of 50 values



Sorted from low to high



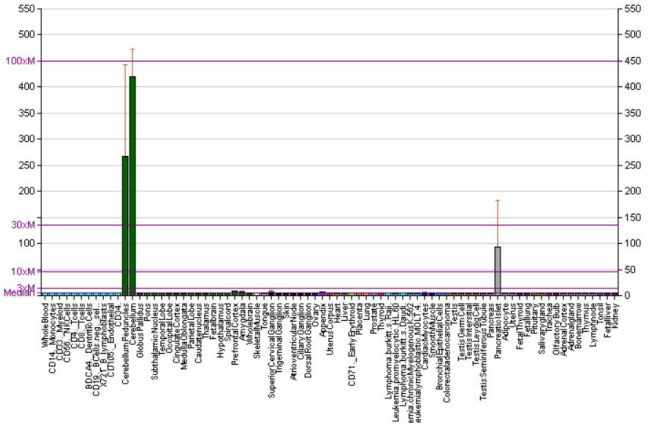
The Gini Index is calculated based on the cumulative distribution



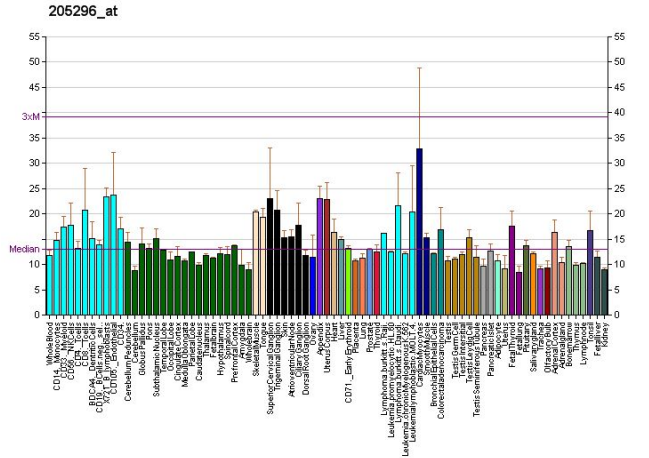
$G=A/(A+B)$

The Gini Index quantifies inequality/ selectivity

NEUROD1

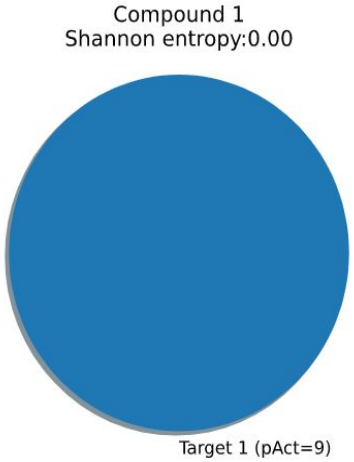


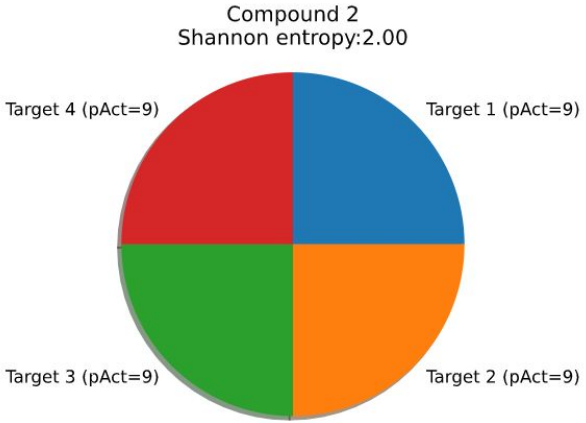
RBL1

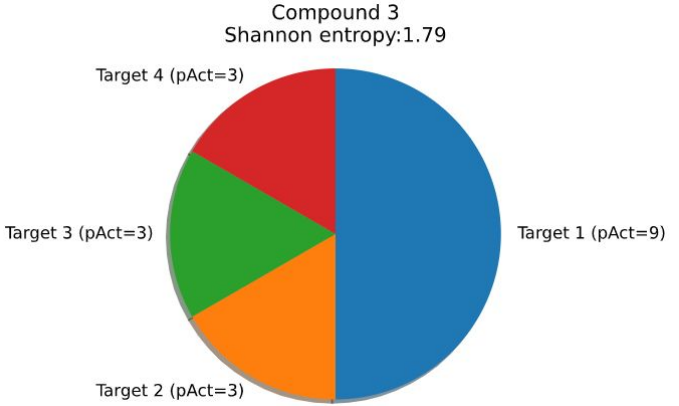


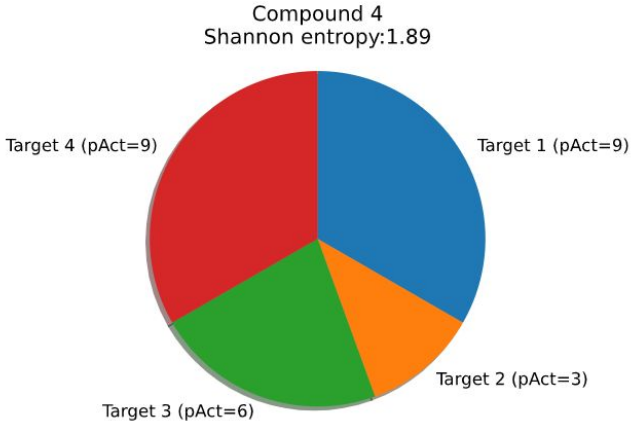
The Gini Index of expression of *NEUROD1* across tissues is near 1, whereas that of *RBL1* is near 0.

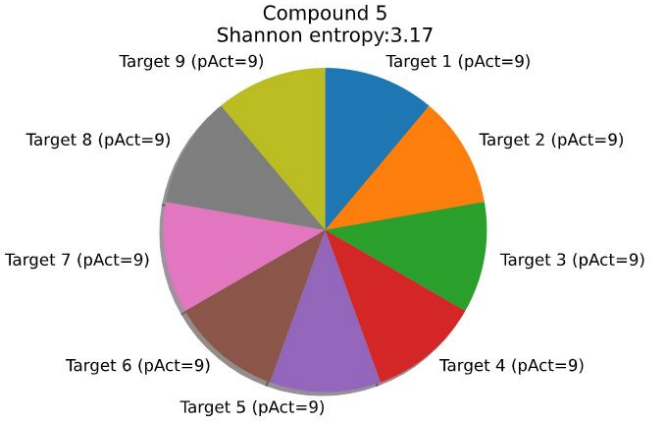
An alternative metric: Shannon's Entropy



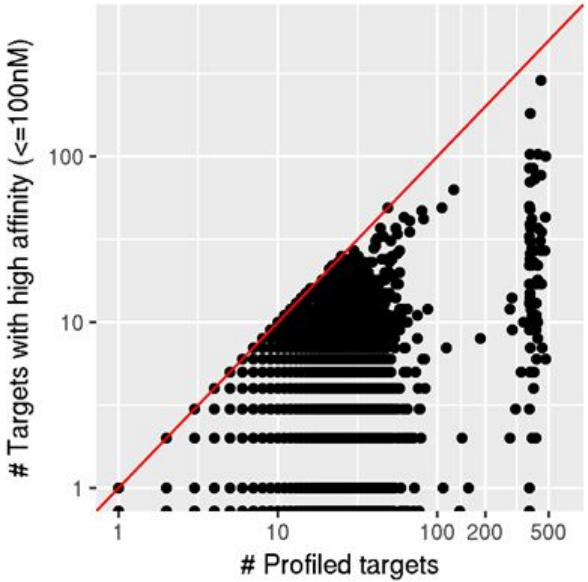


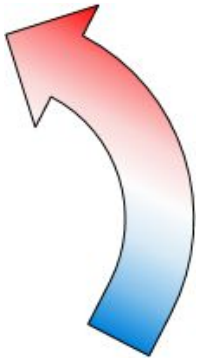


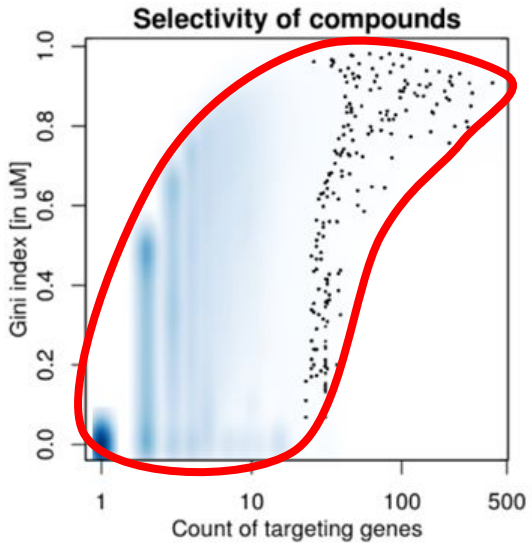




Count of targets and selectivity of ChEMBL molecules



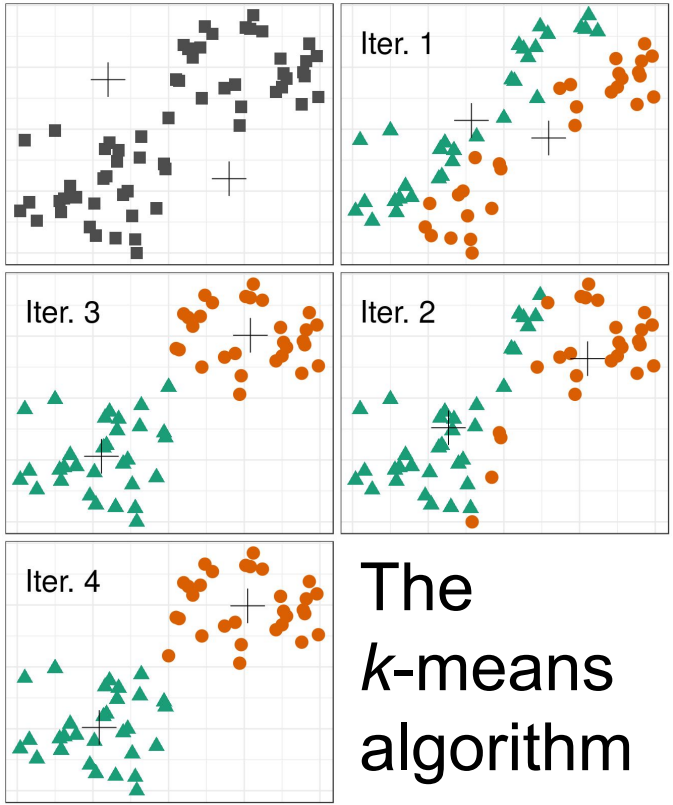




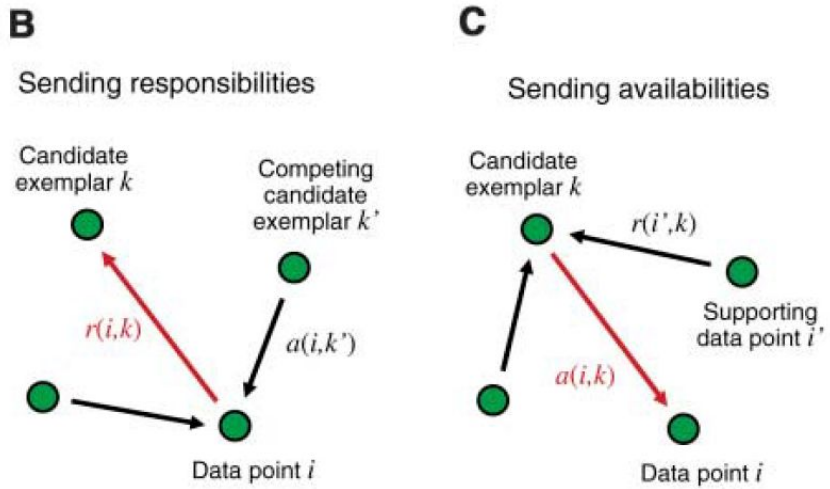
With some exceptions, most compounds are profiled against <100 targets. We distinguish between specific and pleiotropic compounds.

The **shark-fin shape** curve suggests that frequently profiled compounds tend to be more selective (and *vice versa*).

Unsupervised clustering

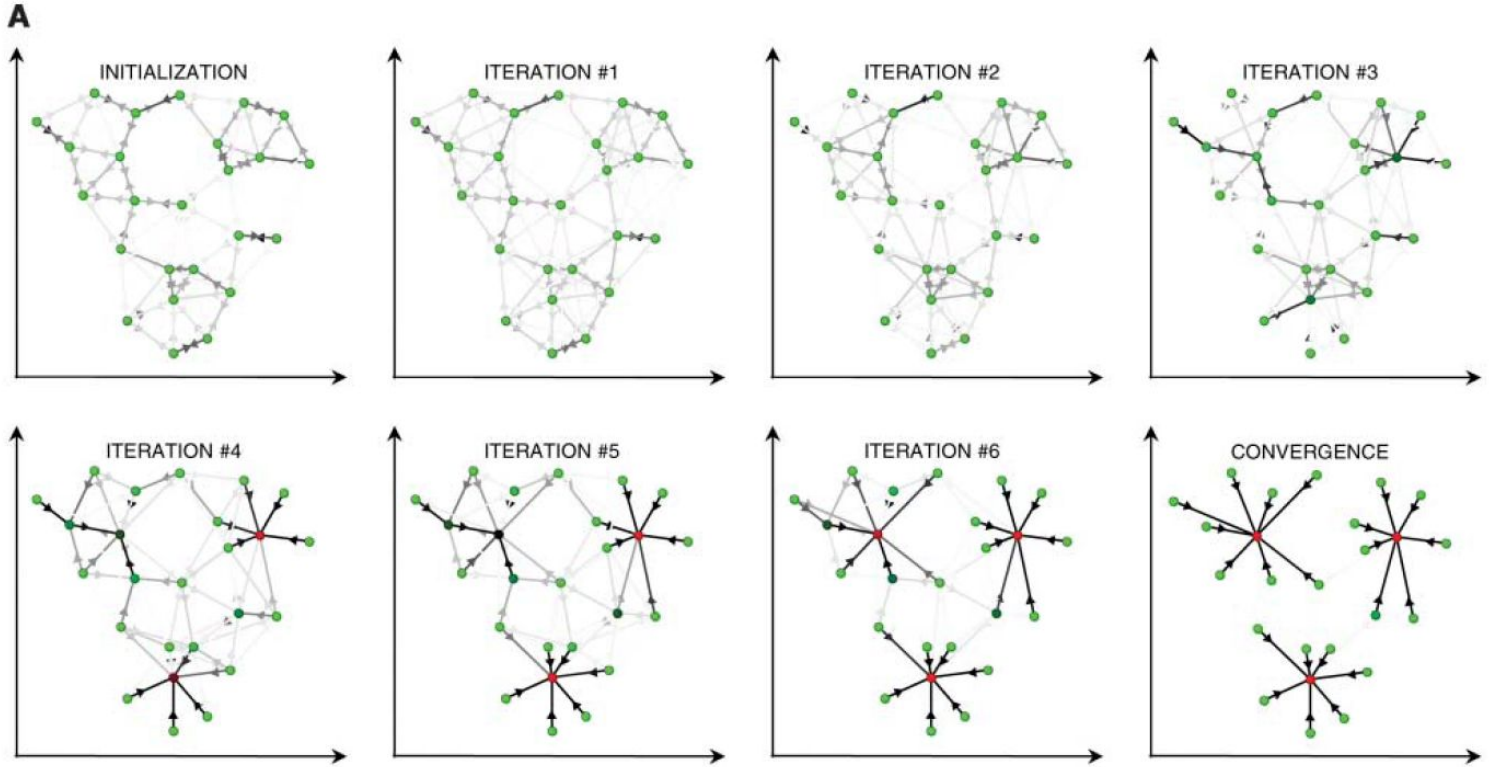


The *k*-means algorithm



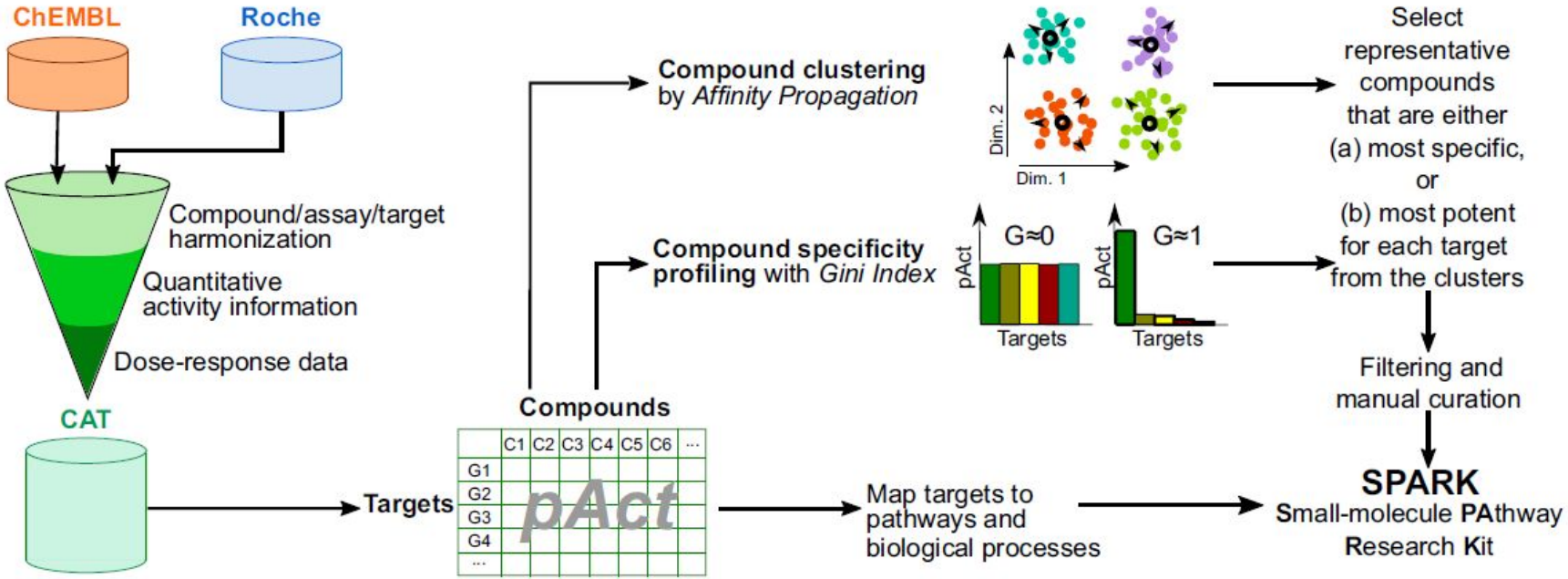
Affinity Propagation updates **responsibilities** and **availabilities** iteratively

Affinity Propagation in action



A movie of iterations

Construction of SPARK in detail



Harmonization

… of public and Roche internal data

Machine learning

… to select compounds

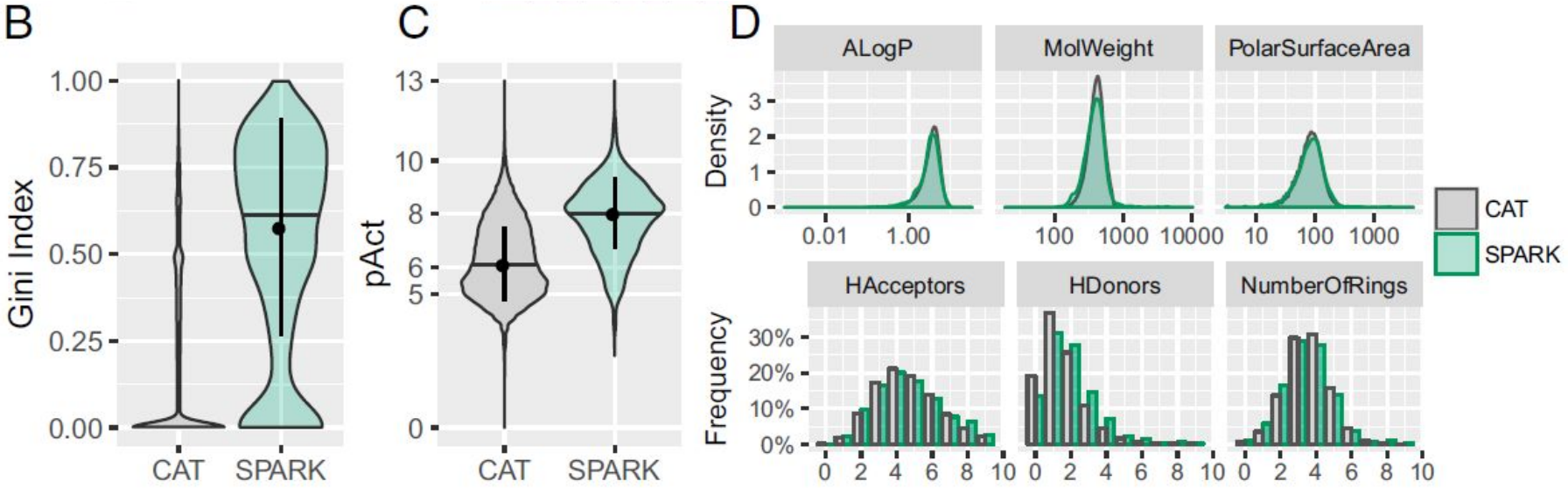
Pathways

… mapped to compounds

Curation

… to enrich quality compounds

SPARK covers the chemical space evenly with representative, potent, and specific compounds

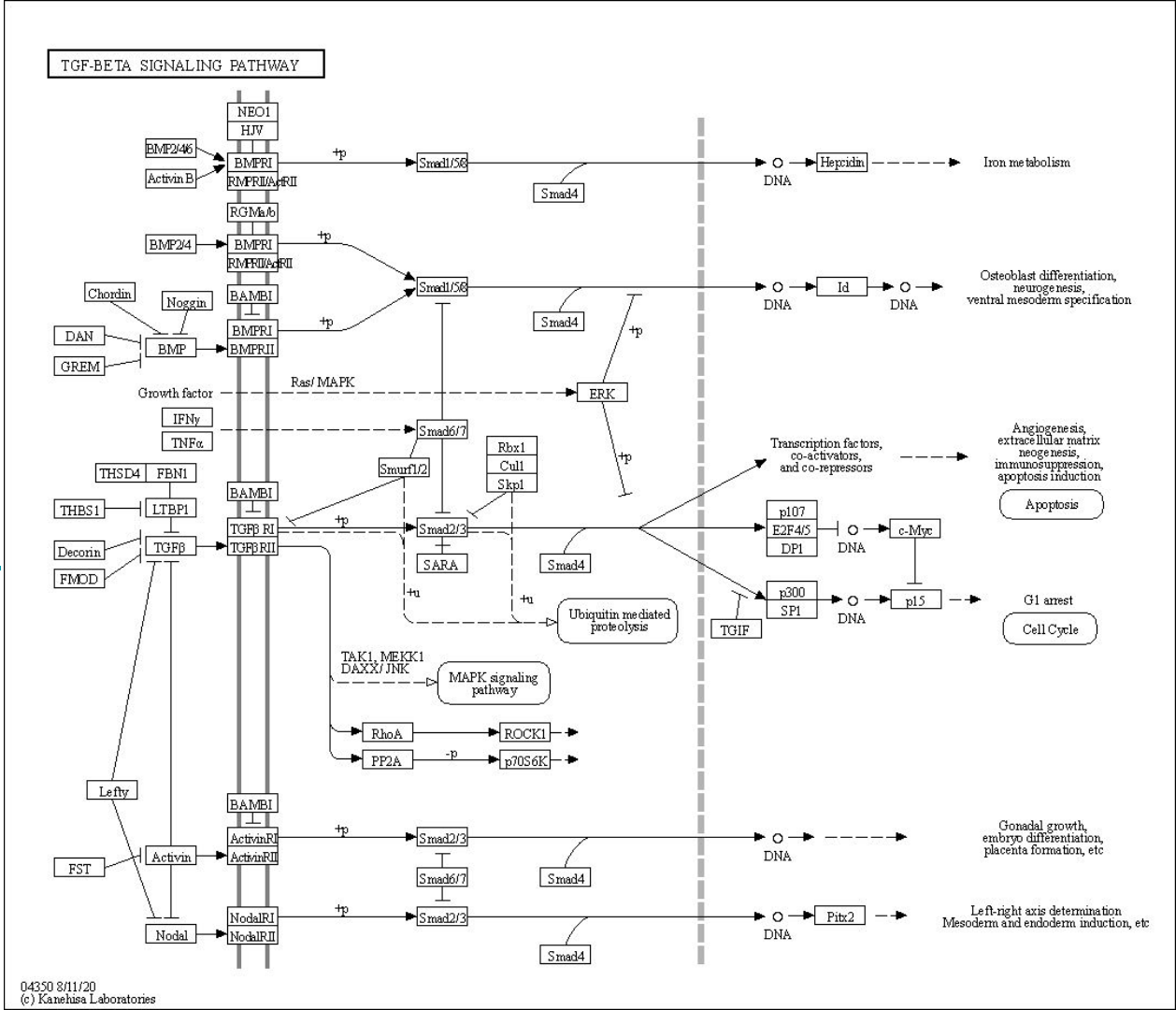


Roudnicky *et al.*, PNAS, 2020, https://www.pnas.org/content/early/2020/08/04/1911532117

Mapping genes to biological pathways

Option 1: KEGG pathways, with the example of TGF-β signaling pathway.

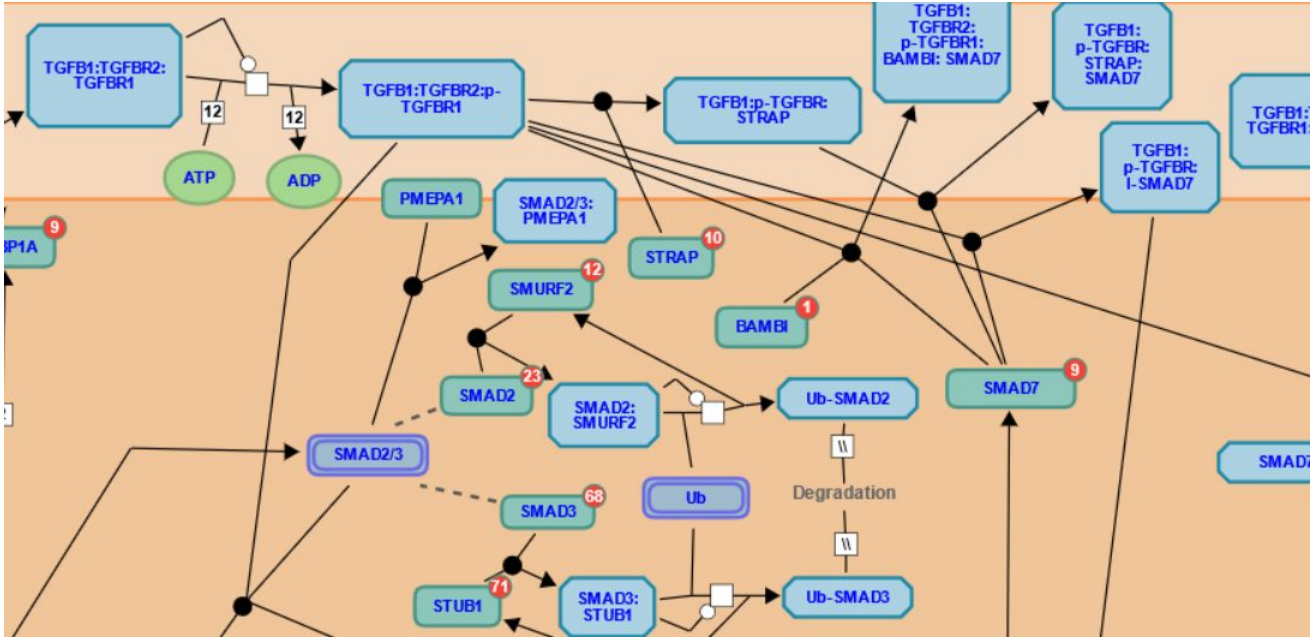
A RESTful API is available for academic use, with clients in Python and R.



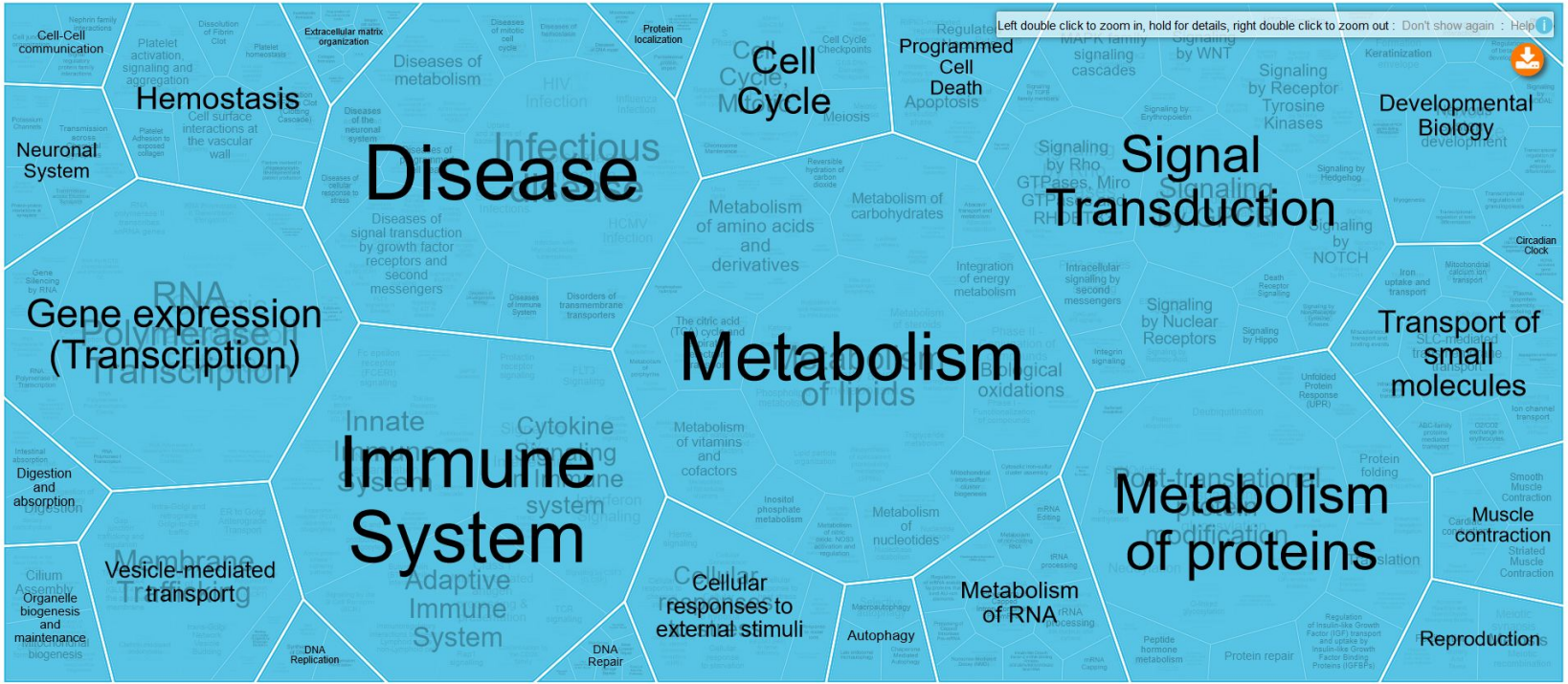
Mapping genes to biological pathways

Option 2: Reactome pathways, with the example of the TGF-β signaling pathway.

Developer's Zone provides API and graph database interfaces.



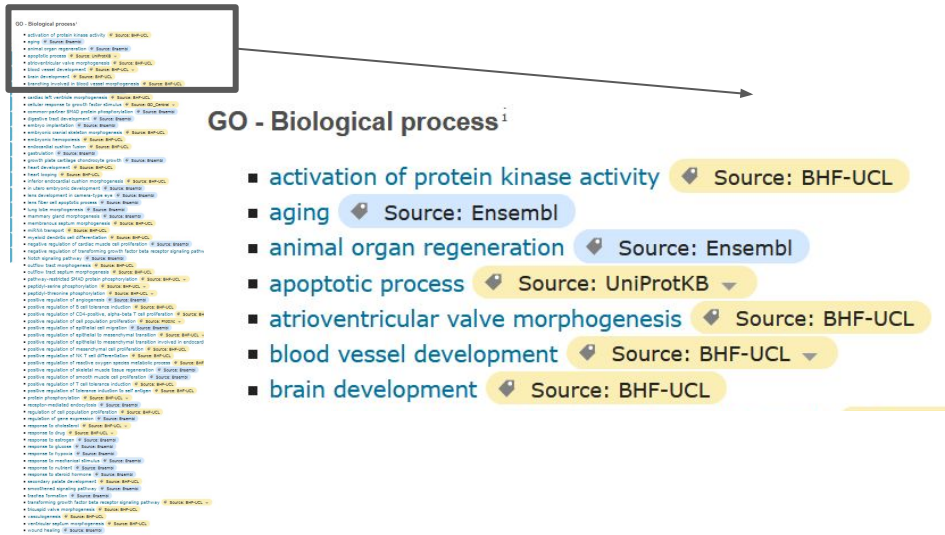
Overview of pathways captured by Reactome



The Voronoi (Reacfoam) view of all pathways in Reactome

Mapping genes to biological processes

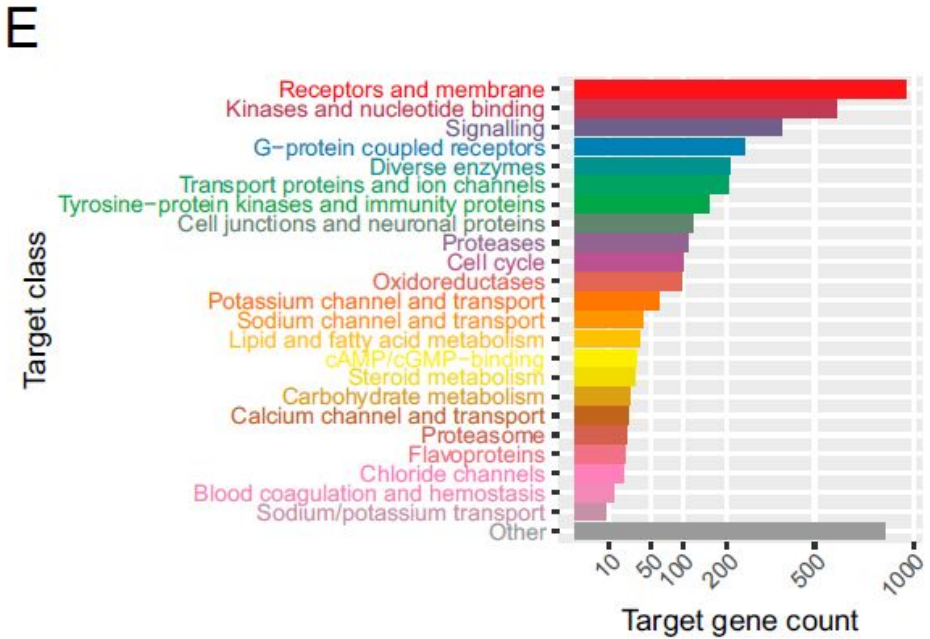
- Gene Ontology
- UniProtKB keywords
- Example: TGFBR2_HUMAN (TGF-beta receptor type -2, P37173)

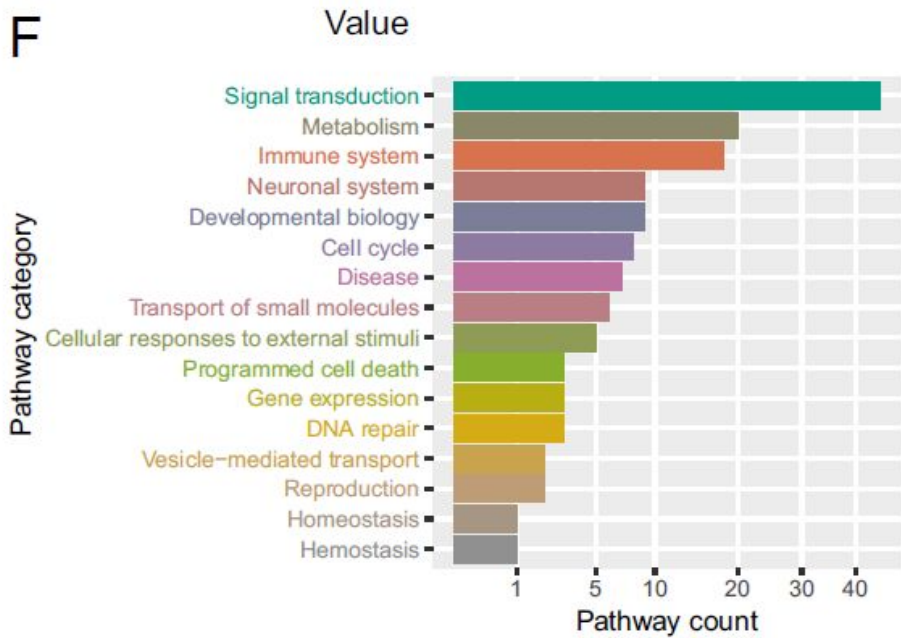


Keywords

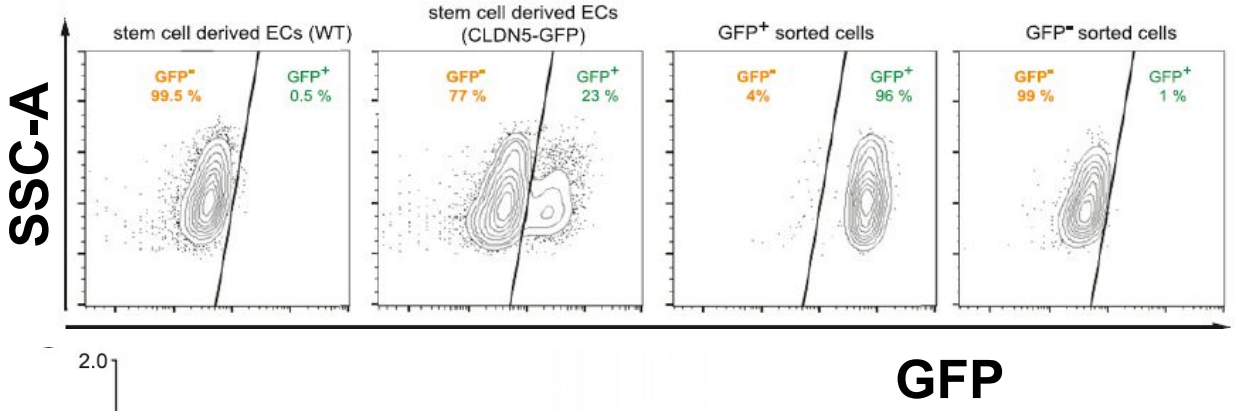
Molecular function	Kinase, Receptor, Serine/threonine-protein kinase, Transferase
Biological process	Apoptosis, Differentiation, Growth regulation
Ligand	ATP-binding, Magnesium, Manganese, Metal-binding, Nucleotide-binding

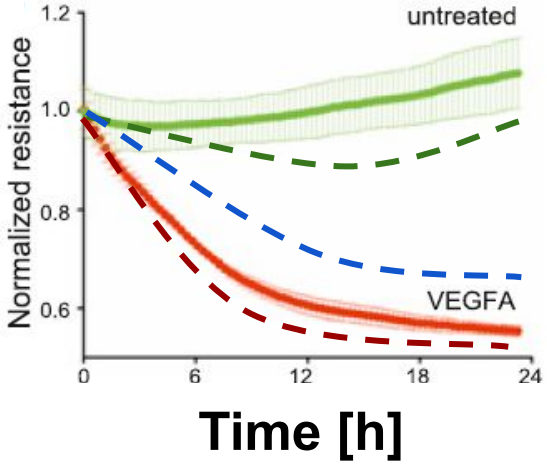
SPARK covers the target space evenly with representative, potent, and specific compounds

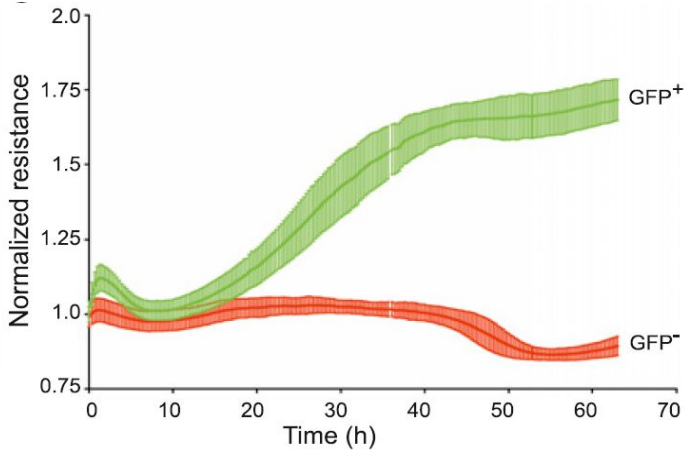




Screening with stem-cell-derived endothelial cells with a reporter added by genome editing





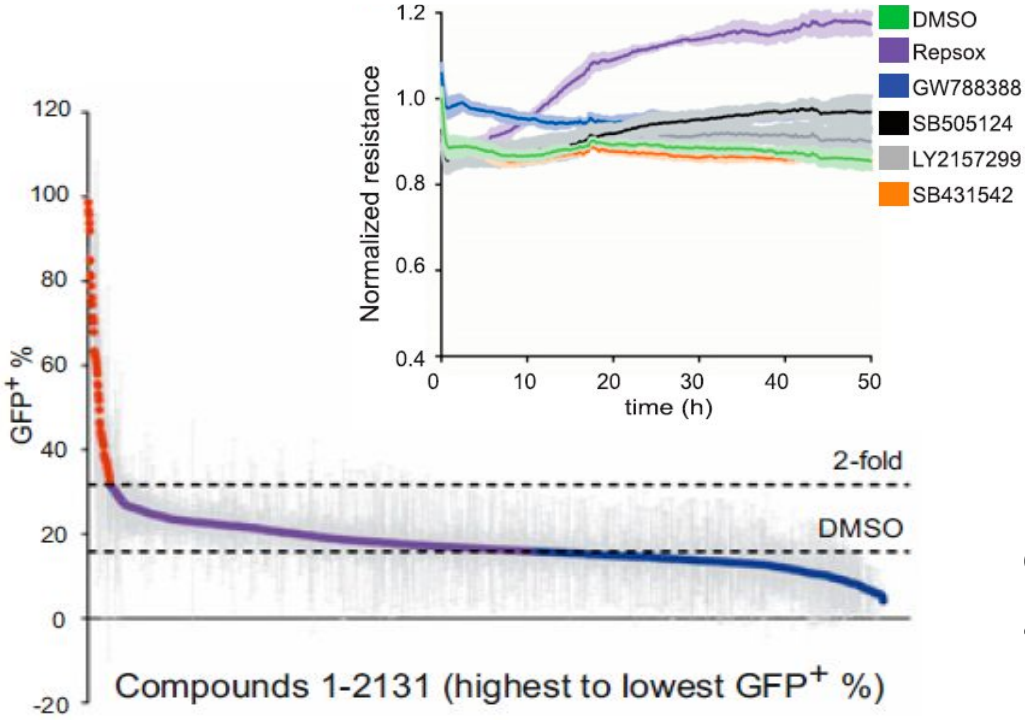


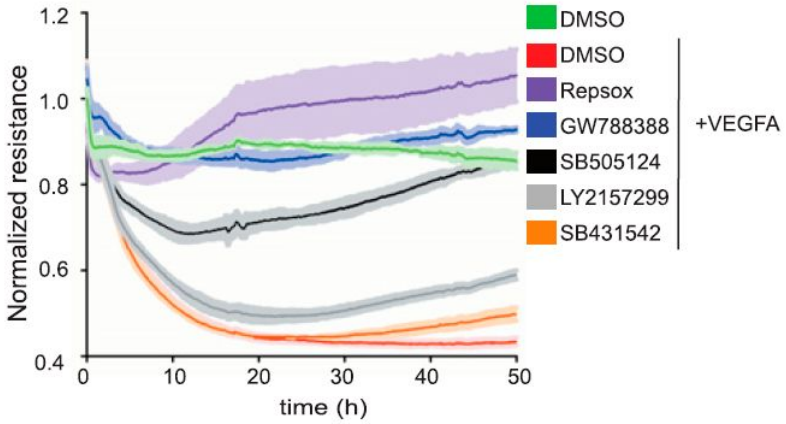
SSC-A: Side-scatter area of flow cytometry;

GFP: Green fluorescent protein;

VEGFA: vascular endothelial growth factor A

Compounds targeting the TGF-β pathway such as RepSox modulates endothelial cells

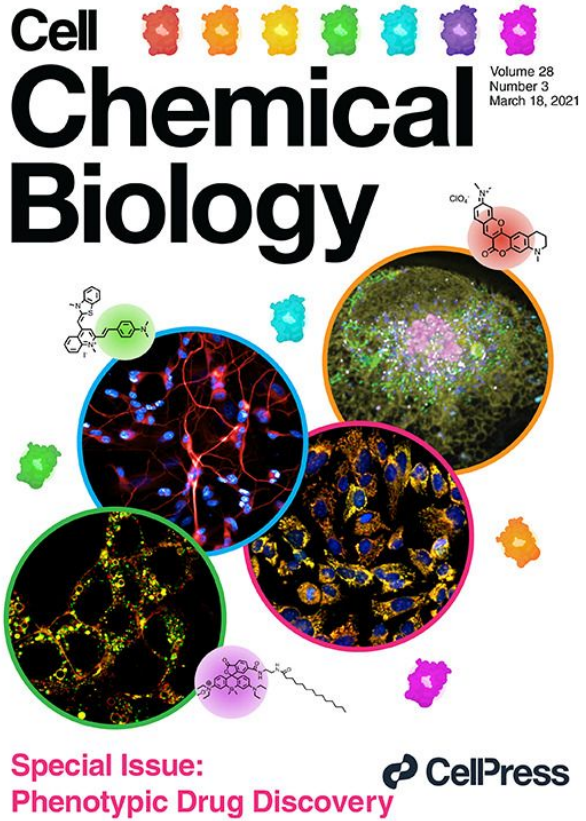




Further *in vitro* and *in vivo* experiments establish RepSox as a tool compound modulating retinopathy.

Conclusions about chemogenomic library

- Phenotypic drug discovery can lead to first-in-class drugs with novel mechanisms;
- Unsupervised machine learning and data modelling contribute to build chemogenomic libraries;
- We can link drug candidates via targets to biological pathways and processes.



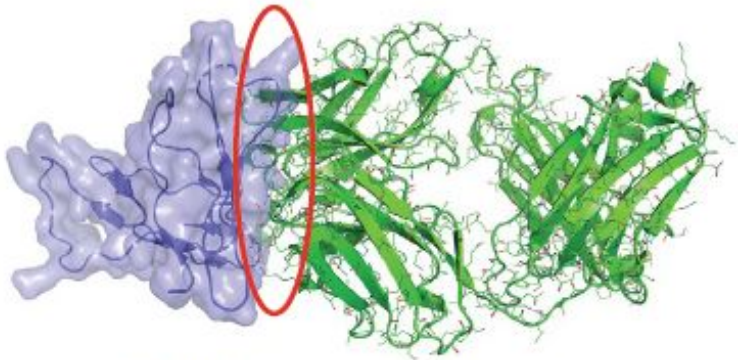
Offline activities of Module II

Please use your favourite programming language (shell scripts, python, R, for instance) and APIs (Application Programming Interfaces) of databases to perform following operations. Submit your code.

1. Retrieve all approved drugs from the ChEMBL database, sort them by approval year and name (a Python example is here; documentations of the ChEMBL API can be found here);
2. For each approved drug **since 2011** that you identified in step (1), retrieve a list of UniProt accession numbers, namely protein targets associated with the drug;
3. For each protein with a UniProt accession number that you identified in step (2), retrieve UniProt keywords associated with it. You can use the UniProt API, documented here. Python and R clients are also available.

Multispecific Drug Use or Target Interactions

b Conventional drug:
- Forms 1 drug–target interface
- Can act throughout body
- Only works if its binding to target alters function of target

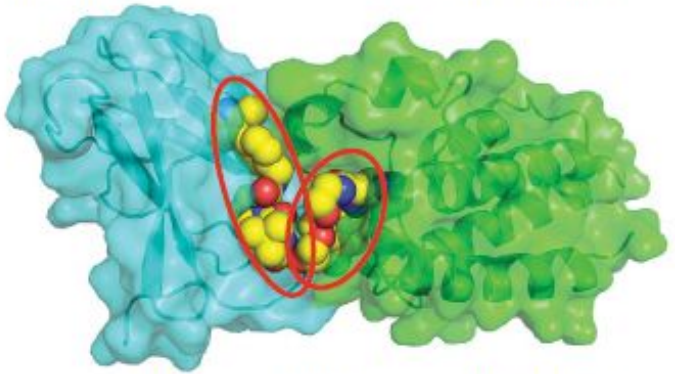


IL-2Rα Basiliximab

c Obligate multispecific drug:
- Forms 2 or more drug–target interfaces

Class 1 'tetherbodies'
- Enrich drug at relevant site of action

Class 2 'matchmakers'
- Link drug to a biological effector



VHL MZ1 $BRD4^{BD2}$

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